REMARKS

Favorable reconsideration is respectfully requested in view of the following remarks.

I. CLAIM STATUS

Claims 1-12 were pending in this application when last examined.

Claims 1-4 and 9-11 were examined on the merits and stand rejected.

Claims 5-8 and 12 were withdrawn as non-elected subject matter.

II. OBVIOUSNESS REJECTION

On page 3 of the Office Action, claims 1-4 and 9-11 remain rejected under 35 U.S.C. § 103(a) as obvious over Graham, Fu and Chen.

This rejection is respectfully traversed.

The claims are directed to a method of constructing a recombinant adenovirus vector of about 38 kb comprising an adenovirus genome DNA of about 33-34 kb and an expression cassette of about 4-5 kb, which comprises: (i) constructing a recombinant cosmid/adenovirus vector of about 45 kb by inserting a DNA sequence of about 7 kb and the expression cassette of about 4-5 kb into the adenovirus genome DNA at a deletion site of an E1 region or both E1 and E3 regions of the adenovirus genome DNA, wherein the DNA sequence consists of a cosmid sequence having recombinase recognition sequences at both ends and outer sequences extended from outer sides of the recombinase recognition sequences, and at least one of the outer sequences has a cloning site for insertion of the expression cassette; (ii) cotransfecting the recombinant cosmid/adenovirus vector and a recombinase-expression vector into cells producing adenovirus E1 protein; and (iii) deleting the cosmid vector sequence from the recombinant cosmid/adenovirus vector but retaining the outer sequences therein, to produce the recombinant adenovirus vector of about 38 kb comprising the adenovirus genome DNA of about 33-34 kb and the outer sequences into which the expression cassette of about 4-5 kb is inserted.

On page 3 of the Action, it was indicated that Graham teaches the invention as essentially claimed.

In reply thereto, it is again respectfully submitted that the cited art references fail to teach each and every element of the claimed invention, and they lack a suggestion/motivation to combine their teachings to arrive at the claimed invention with a reasonable degree of success.

In particular, the method in Graham is discussed in the instant application at page 3, last paragraph, to page 4, second paragraph. In particular, Graham describes a method for constructing a recombinant adenovirus vector using a circular DNA constructed by inserting a small plasmid at the restriction enzyme Xba I site, which site exists at the one location in the E1 region of the adenovirus 5 type, and then transfection to a mammalian cell line (the 293 cells). It was reported that the circular DNA produces the infectious virus. See also the Abstract on page 2917 of Graham. The article suggests that a recombinant adenovirus vector can be constructed by replacing the E1 region or E3 region of a circular adenovirus DNA with an exogenous gene.

However, the method in Graham differs from that of the instant invention in that when a recombinant adenovirus vector is actually constructed according to the method in Graham, two problems arise. The first problem is the low efficiency in incorporating the expression cassette into the extremely large plasmid which contains the adenovirus genome DNA. The second is plasmid DNA portions remain in the constructed adenovirus vector. See page 4, lines 6-12 of the disclosure.

It is respectfully submitted that these two problems were recognized and solved by Applicants with the present invention. In particular, the method of the present invention overcomes these problems, because it does not have a low efficiency of incorporating the expression cassette and it deletes the cosmid vector. The deletion of the cosmid sequence means that the result recombinant adenovirus vector does not retain the plasmid DNA portions as in Graham. Thus, the method of the present invention results in a structurally different recombinant adenovirus vector from that in Graham. Therefore, in contrast to the assertion made in the Action, Graham does not teach the invention as essentially claimed.

Also, Fu et al. only solved the first problem noted above with regard to the Graham method. In particular, Fu et al. teach cosmids that are able to handle the large size of adenovirus DNA. An expression cassette may be more efficiently incorporated into the cosmid adenovirus vector "adCOS" than that of Graham.

Fu et al. did not solve the second problem with respect to the method in Graham. In this regard, the vector Ad COS in Fu et al. comprises "adenovirus DNA" and "cosmid sequence".

At the time of filing of the invention, a first objective in the art was to construct a recombinant adenovirus having infectious ability to mammalian cells. Graham accomplished this objective. The plasmid based vector "Ad5" of Graham contains about 36kb-34kb of adenovirus DNA and 2kb of plasmid DNA and it is infectious to mammalian cells.

After the teachings in Graham, a second objective in the art was to solve the stability problem in the plasmid based adenovirus vector. Fu et al. accomplished this object by using a cosmid vector.

However, Fu et al. did not recognize or solve the second above-noted problem with regard to the method in Graham, *i.e.*, the problem of plasmid DNA portions remaining in the constructed adenovirus vector.

Moreover, in reply to the Office's position on page 4 of the Action that the E1 and E3 deletions were well known in the art and one of ordinary skill in the art could approximate the size of the viral vectors and inserts recited in the claims, Graham teaches that the size of Ad5 vector is 36 kb and it can only take 2kb extra DNA. Please see the description of Figure 1 on page 2917 of Graham, wherein Graham discloses the maximum size of DNA which can be inserted into Ad5 DNA without exceeding packaging constraints is 2kb. Accordingly, prior to the instant invention, the state of the art was such that: (i) a recombinant adenovirus vector should be limited in size to within 38kb in order to maintain the ability to infect animal cells and produce infectious virus particles; and (ii) an expression cassette to be incorporated into the Ad5 vector should be within 2kb.

In contrast, the size of adCOS in Fu et al is about 40kb, which exceeds the recommended 38 kb limit. Accordingly, in view of above (i) & (ii), one of ordinary skill in the art at the time of

the invention would believe the vector adCOS in Fu et al. is not infectious and cannot take any further extra DNA.

Thus, in contrast to Office's position on page 4 of the Action that the E1 and E3 deletions were well known in the art, and thus, one of ordinary skill in the art could approximate the size of the viral vectors and inserts recited in the claims, the references lacked a reasonable expectation of success of modifying their teachings to arrive at the claimed invention of a recombinant adenovirus of about 38kb containing an expression cassette of about 4-5kb, because Graham teaches only 2kb can be inserted (not 4-5kb) and a recombinant adenovirus vector should be limited in size to within 38kb (not 40kb as in Fu et al.).

It is again emphasized that at the time of invention, a need for deletion of base vector (plasmid or cosmid) had not been recognized in the art. The present Applicants recognized that the deletion of a base vector is essential for constructing an infectious recombinant adenovirus containing a large-sized expression cassette. As an embodiment of this idea, the present invention provides a recombinant adenovirus of about 38kb containing an expression cassette of about 4-5kb. Thus, as evident from the Examples of the instant disclosure, the adenovirus vector of the present invention is about 38 kb and retains the ability to infect animal cells and produce infectious virus particles.

Chen et al. also fail to disclose the structural components of the claimed adenovirus vector. Chen et al. also fail to recognize and solve the above-noted problems associated with the method in Graham. The reference is relied upon for disclosing the action of different recombinases on the adenovirus genome. Chen et al. mention nothing regarding the insertion site of the expression cassette nor the specific structural components of the adenovirus vector of the claimed invention. Thus, in a situation where the necessity for deletion of a base vector has not been recognized, one of ordinary skill in the art would not conceive of the idea of using the recombination system of Chen et al.

Therefore, the obviousness rejection of claims 1-4 and 9-11 under 35 U.S.C. § 103(a) over Graham, Fu and Chen is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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